



SARIMA-modelled greater severity and mortality during the 2010/11 post-pandemic influenza season compared to the 2009 H1N1 pandemic in English hospitals



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ABSTRACT

Objective: The COVID-19 pandemic demonstrates the need for understanding pathways to healthcare demand, morbidity, and mortality of pandemic patients. We estimate H1N1 (1) hospitalization rates, (2) severity rates (length of stay, ventilation, pneumonia, and death) of those hospitalized, (3) mortality rates, and (4) time lags between infections and hospitalizations during the pandemic (June 2009 to March 2010) and post-pandemic influenza season (November 2010 to February 2011) in England.

Methods: Estimates of H1N1 infections from a dynamic transmission model are combined with hospitalizations and severity using time series econometric analyses of administrative patient-level hospital data.

Results: Hospitalization rates were 34% higher and severity rates of those hospitalized were 20%–90% higher in the post-pandemic period than the pandemic. Adults (45–64-years-old) had the highest ventilation and pneumonia hospitalization rates. Hospitalizations did not lag infection during the pandemic for the young (<24-years-old) but lagged by one or more weeks for all ages in the post-pandemic period.

Discussion: The post-pandemic flu season exhibited heightened H1N1 severity, long after the pandemic was declared over. Policymakers should remain vigilant even after pandemics seem to have subsided. Analysis of administrative hospital data and epidemiological modelling estimates can provide valuable insights to inform responses to COVID-19 and future influenza and other disease pandemics.

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Introduction

Since the turn of the 21st century, countries worldwide have encountered multiple health emergencies, including the 2003 SARS epidemic, 2009 influenza A/H1N1 pandemic, 2014 Ebola epidemic, and the ongoing 2019 COVID-19 pandemic, which led to steep and sudden surges in healthcare demand as well as high mortality and morbidity. In this most recent pandemic, the need for rapid response to the influx of COVID-19 patients was first evidenced by China's construction of two 1000-bed hospitals in

Wuhan (Qin, 2020) followed by overflowing hospitals and critical care facilities in Lombardy (Cockburn, 2020), New York City (Feuer, 2020), and the United Kingdom (Mueller, 2021).

In order to understand how future pandemics of novel influenza viruses burden hospitals and critical care facilities, policymakers need a comprehensive understanding of patient severity, patient flows and clinical pathways. Namely, they need to know (1) hospitalization rates of those who are infected, (2) the severity of those who are hospitalized, and (3) the mortality of infected, hospitalized, and severe patients. During a pandemic, it is very difficult to obtain reliable estimates of the pandemic's burden to healthcare systems because real-time surveillance is often insufficient for such forecasts. While variations in estimates of H1N1 hospitalization rates (defined as hospitalizations divided by infection incidence) vary significantly worldwide, possibly due to country-specific differences, estimates vary even within England

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from 310 (Campbell et al., 2011) to 546 (Presanis et al., 2011) hospitalizations per 100,000 infections. H1N1 hospitalization fatality rates in China range from 28.9 in Beijing (Wu et al., 2017) to 9.9 deaths per 100,000 population in Hefei (Liu et al., 2017). Case fatality rates (deaths divided by infections) in England range even more widely from 10 (Campbell et al., 2011) to 4582 (Mytton et al., 2012) deaths per 100,000 infections. Although country-specific differences could not be ascertained for H1N1 ventilation and pneumonia hospitalization rates due to the minimal literature, global estimates still differ: from 5340 (Capelastegui et al., 2012) to 24,809 (Louie et al., 2009) to 81,000 (Maves et al., 2019) ventilations per 100,000 H1N1 hospitalizations. Similarly, studies range from 4228 (Louie et al., 2009) to 13,286 (Campbell et al., 2011) to 19,000 (MacIntyre et al., 2018) H1N1 hospitalizations with a pneumonia co-infection per 100,000. These wide variations can be explained by differences in testing regimes across hospitals and community settings, asymptomatic infections which leave many patients undiagnosed, differences in hospital practices, small and unrepresentative samples, and other factors (Bolotin et al., 2012; Campbell et al., 2011; Capelastegui et al., 2012; Kwok et al., 2017; Reed et al., 2009; Shrestha et al., 2011).

This paper uses the 2009 H1N1 pandemic, as the most recent historical influenza pandemic, to provide robust estimates for hospitalization rates (i.e. proportion of infections treated in hospital), the severity of hospitalizations, mortality rates, and time lags between symptoms onset and hospitalization during the pandemic and 2010/11 post-pandemic influenza season in England. We overcame previous data limitations by using consistent estimates from two separate studies: incidence of all H1N1 infections in England from a mathematical model of influenza transmission (Dorigatti et al., 2013) and all H1N1 hospitalizations in England calculated using time series econometric analyses from Hospital Episode Statistics (HES) administrative inpatient data (Lau et al., 2019). Additionally, time series forecasting methods were used on HES data to determine severity of those H1N1 hospitalizations. Finally, temporal cross-correlation analysis was performed to measure time lags between H1N1 infections and hospitalizations.

Previous literature suffered from data and methodological limitations that resulted in inaccurate estimates of the pandemic's burden on hospitals. While there are of course significant differences between the H1N1 and COVID-19 pandemics, including disease type, transmissibility, and scale of outbreak, there exists a clear need to provide policymakers with better estimates of hospitalization rates, lags between incidence and admissions, and the severity of those admissions with regard to morbidity and mortality in order to inform health system capacity planning and resource allocations during health emergencies. This study demonstrates that the use of comprehensive data on H1N1 infections and sophisticated time series econometrics to extract H1N1-specific hospitalizations, severity, and mortality improves upon previous literature. These data and methods can thus be further applied to new data to help policymakers better prepare for the COVID-19 pandemic and future influenza and other disease pandemics.

Data

In total, six weekly time series datasets covering the pandemic and post-pandemic influenza season were created: (1) H1N1 infections taken from Dorigatti and colleagues (Dorigatti et al., 2013), (2) Influenza-like Illness (ILI) hospitalizations from Lau and colleagues (Lau et al., 2019), (3) average length of stay (aLOS) for ILI hospitalizations, (4) ventilation-associated ILI hospitalizations, (5) pneumonia-associated ILI hospitalizations, and (6) ILI

hospitalization mortality. For each dataset, separate analyses on pandemic and post-pandemic time periods for all ages and stratified by age (except mortality due to data limitations) were performed, totalling 72 time series.

Weekly age-stratified H1N1 infections in England were estimated following Dorigatti and colleagues (Dorigatti et al., 2013). The study used syndromic data consisting of weekly ILI consultation data from QSurveillance, a real time clinical surveillance system of 4200 general practices (GPs) in the UK, virological data from the Royal College of General Practitioners and the Health Protection Agency (HPA) Regional Microbiology Network, and serological data from the HPA in England collected during the pandemic (May 2009 to January 2010) and the post-pandemic influenza season (September 2010 to February 2011). A deterministic transmission model was first defined for each age-group building on a susceptible, infected, and recovered (SIR) model that accounts for social contact patterns, age-group population sizes, vaccination coverage, time from infection or vaccination to seroconversion, and reporting rate to GPs for ILI. This was extended to form a statistical model to jointly analyze the ILI, virological, and serological data. The joint posterior distribution of parameters was characterized using Markov Chain Monte Carlo (MCMC) sampling in a Bayesian setting. This resulted in two time series of $N = 88$ weeks of the number of H1N1 infections during the pandemic and post-pandemic period for all ages combined (overall) and for six age-groups, totalling 14 time series.

Weekly age-stratified H1N1 hospitalizations in England were estimated following Lau et al. (2019). The study used Hospital Episode Statistics (HES) for Admitted Patient Care (APC), a patient-level administrative records dataset containing all inpatient hospitalizations to the NHS ($N = 132,532,270$) in England from April 2004 to February 2011. HES APC includes patient diagnoses following the International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10); age; length of stay; procedures, operations, and interventions using the Office of

Table 1

List of ILI ICD-10 codes and ventilation OPCS Classification of Interventions and Procedures version 4.2 codes.

Code	Description
ICD-10	
J09	Influenza due to identified zoonotic or pandemic influenza virus
J10	Influenza due to identified seasonal influenza virus
J10.0	Influenza with pneumonia, seasonal influenza virus identified
J10.1	Influenza with other respiratory manifestations ^a , seasonal influenza virus identified
J10.8	Influenza with other manifestations ^b , seasonal influenza virus identified
J11	Influenza, virus not identified
J11.0	Influenza with pneumonia, virus not identified
J11.1	Influenza with other respiratory manifestations ^a , virus not identified
J11.8	Influenza with other manifestations ^b , virus not identified
OPCS 4.2	
E85.1	Invasive mechanical ventilation
E85.2	Non-invasive mechanical ventilation (not elsewhere classified) ^c
E85.3	Improving efficiency of ventilation
E85.4	Bag valve mask ventilation
E85.5	Nebuliser ventilation
E85.8	Other specified ventilation support
E85.9	Unspecified ventilation support

^a Other respiratory manifestations refer to acute upper respiratory infection, laryngitis, pharyngitis, pleural effusion.

^b Other manifestations refer to encephalopathy due to influenza, gastroenteritis, acute myocarditis.

^c Includes continuous positive airway pressure, intermittent positive pressure ventilation, negative pressure ventilation, bi-level positive airway pressure.

Population Censuses and Surveys Classification of Surgical Operations and Procedures, 4th revision (OCPS-4.2) codes; and deaths. All ILI hospitalizations (N = 29,403 across 251 hospitals) with ICD-10 codes J09 (certain identified influenza), J10 (seasonal influenza), and J11 (unidentified influenza) as a primary or secondary diagnosis between April 2004 and February 2011 were extracted (Table 1).

From the sample of all ILI hospitalizations, we extracted unique datasets for four severity indicators: 1) average LOS, 2) hospitalizations requiring ventilation, 3) hospitalizations diagnosed with pneumonia, and 4) hospitalizations resulting in death. Each dataset was collapsed by week to generate separate time series of N = 410 weekly ILI hospitalizations for aLOS, ventilation, pneumonia, and deaths. LOS was calculated as the number of days between the patient's admission and discharge, including transfers between hospitals. The variable was attributed to the patient on admission day, covering the entire duration of the hospitalization including those that spanned across two or more weeks (e.g. a hospitalization starting in week 22 that lasts 14 days and ends in week 24 would have a LOS value of 14 in week 22). A time series of weekly aLOS for all N = 29,403 ILI hospitalizations was created. We then computed the weekly number of hospitalizations utilizing ventilation, with pneumonia, and resulting in death. We identified N = 2167 ILI hospitalizations with a ventilation-related OPCS-4.2 code (Table 1); N = 2337 ILI hospitalizations also diagnosed with pneumonia (following Kaselitz et al., 2019 by using ICD-10 codes J12–J18); and N = 1526 ILI hospitalizations resulting in death.

Analysis

Our study addresses three questions: (1) of those individuals who were infected with H1N1, how many were hospitalized?; (2) of those individuals hospitalized, how many suffered from pneumonia, were ventilated, and how long was their length of stay?; and (3) of those affected by H1N1 (infected or generally/severely hospitalized), how many died? About 3 in 4 H1N1 hospitalizations were recorded as unspecified ILI cases in the data. Time series forecasting has been used in previous literature to estimate excess H1N1 mortality (Thompson et al., 2009) and, more recently, confirmed and recovered COVID-19 cases (Maleki et al., 2020). Therefore, we used multiplicative seasonal autoregressive integrated moving average (SARIMA) models to establish a counterfactual of ILI hospitalizations and four severity indicators in a non-pandemic year. The differences between observed values and these estimates were considered in excess of typical, non-pandemic years and therefore attributed to H1N1. Excess severity was measured in terms of excess ILI hospitalizations with ventilation, pneumonia, and deaths as well as excess average weekly LOS.

SARIMA models, a seasonal variation of ARIMA to overcome the seasonality typically found in influenza, linearly fit to a stationary time series and predict future observations using lags of observations (autoregression) and lags of error (moving average). Following Box et al. (2015) model building procedures (Lau et al., 2019), we fitted SARIMA models on pre-pandemic data (April 2004 to October 2008) by first taking the difference in weekly data one year apart (e.g. hospitalizations in week 42 of 2008 are compared to hospitalizations in week 42 of 2009) to remove the seasonality and achieve stationarity in our time series. We then selected the number of AR and MA lags to use in each SARIMA model via autocorrelation function and partial autocorrelation function plots, respectively. Akaike Information Criterion and Bayesian Information Criterion were also estimated to help enrich the model selection process. Ljung-Box Portmanteau (Q) tests of autocorrelation of the residuals were run on each SARIMA model to assess goodness-of-fit. These SARIMA models were then used to predict

counterfactuals of weekly non-pandemic ILI hospitalizations and their severity, overall and by age-group, during the pandemic and post-pandemic period (November 2008 to February 2011).

Pandemic weeks were calculated as two or more consecutive weeks where the actual number of ILI hospitalizations exceeded the upper bound of the 95% confidence interval of the SARIMA-generated estimates. A total of 58 SARIMA models were fitted and run: for each hospitalization-related measure and for each pandemic and post-pandemic period, one all-ages and six age-stratified models were run, resulting in 14 models each for hospitalizations, aLOS, ventilation, and pneumonia. For deaths, two all-ages models, one for the pandemic and one for the post-pandemic period, were run. See Appendix B for detailed methods.

From the SARIMA estimates, we calculated the overall and age-stratified total H1N1 hospitalizations and four severity indicators for the pandemic and post-pandemic period. These, combined with aggregated estimates for H1N1 infections across both time periods, were then standardized using official population estimates (Office for National Statistics et al., 2016).

Then, we calculated hospitalization rates; aLOS, ventilation and pneumonia rates among hospitalized patients as well as case, hospitalization, ventilation, and pneumonia fatality rates among infected individuals for the pandemic and post-pandemic period (Table 2). One-way ANOVA and Bonferroni multiple comparison tests were performed to discern any significant differences between age-groups and between the pandemic and post-pandemic flu season (see Appendix C for more details). Confidence intervals for all rates were calculated via bootstrapping, sampling N = 10,000 times with replacement for the pandemic and post-pandemic influenza season separately. The 95% confidence interval was given by the 2.5th and 97.5th percentiles.

Finally, delayed presentation to the hospital following infection can lead to more severe clinical outcomes once the patient reaches the hospital. To evaluate this, we used temporal cross-correlation analysis (Hendriks et al., 2017; Huang et al., 2011) to determine any lags between the estimated incidence of infections and hospitalizations (Appendix D). The weekly H1N1 hospitalization time series was lagged up to 10 weeks before and after the weekly H1N1 infection incidence time series. Cross-correlations were calculated for each lag and the lag with the greatest corresponding cross-correlation, indicating the strongest alignment between both time series, was the most likely lag between infections and hospitalizations.

Results

Young adults (25–44-years-old) made up 31% of H1N1 infections, the largest proportion compared to all other age-groups, followed by adults (45–64-years-old) at 24%. Young adults also had the highest proportion of H1N1 hospitalizations among

Table 2
Hospitalization, severity, and fatality rate calculations.

Variable	Calculation
Hospitalization rate	$\frac{\text{H1N1 hospitalizations}}{\text{H1N1 infections}}$
Ventilation-hospitalization rate	$\frac{\text{H1N1 hospitalizations requiring ventilation}}{\text{H1N1 hospitalizations}}$
Pneumonia-hospitalization rate	$\frac{\text{H1N1 hospitalizations with pneumonia}}{\text{H1N1 hospitalizations}}$
Case fatality rate	$\frac{\text{H1N1 hospitalizations resulting in death}}{\text{H1N1 hospitalizations}}$
Hospitalization fatality rate	$\frac{\text{H1N1 hospitalizations resulting in death}}{\text{H1N1 hospitalizations requiring ventilation}}$
Ventilation fatality rate	$\frac{\text{H1N1 hospitalizations resulting in death}}{\text{H1N1 hospitalizations requiring ventilation}}$
Pneumonia fatality rate	$\frac{\text{H1N1 hospitalizations resulting in death}}{\text{H1N1 hospitalizations with pneumonia}}$

Notes: Numerators and denominators are first calculated by week, then aggregated by pandemic and post-pandemic period, then transformed into rates. Each rate is multiplied by 100,000.

age-groups, while adults comprised the greatest proportion of ventilation (30%) and pneumonia (32%) H1N1 hospitalizations. Elderly ($65\pm$ years-old) had the longest aLOS of 13.42 days ($SD = 11.15$) compared to all other ages. Over all ages, there were on average 3.26 deaths ($SD = 1.69$) per week. See Appendix Table A1 for more descriptive statistics.

We estimated a total of 13,619,803 (95% CI 13,357,069–14,130,071) H1N1 infections and 21,855 (95% CI 20,786–22,890) hospitalizations over the pandemic (June 2009 to March 2010) and post-pandemic period (November 2010 to February 2011) (see population standardized estimates in Appendix Table A2). There were two waves of

transmission during the pandemic, followed by a third post-pandemic wave, reflected in the incidence of infections and hospitalisations (Figure 1). The magnitude and timing of incidence and hospitalization waves differed between age-groups. For 5–14-year-olds, the incidence peak during the first pandemic wave was twice as high as during the post-pandemic wave; hospitalization peaks were similar in both time periods. Older age-groups, however, had higher incidence and hospitalization peaks during the post-pandemic flu season compared to the pandemic.

Although the overall number of infections was lower during the post-pandemic influenza season compared to the pandemic, the

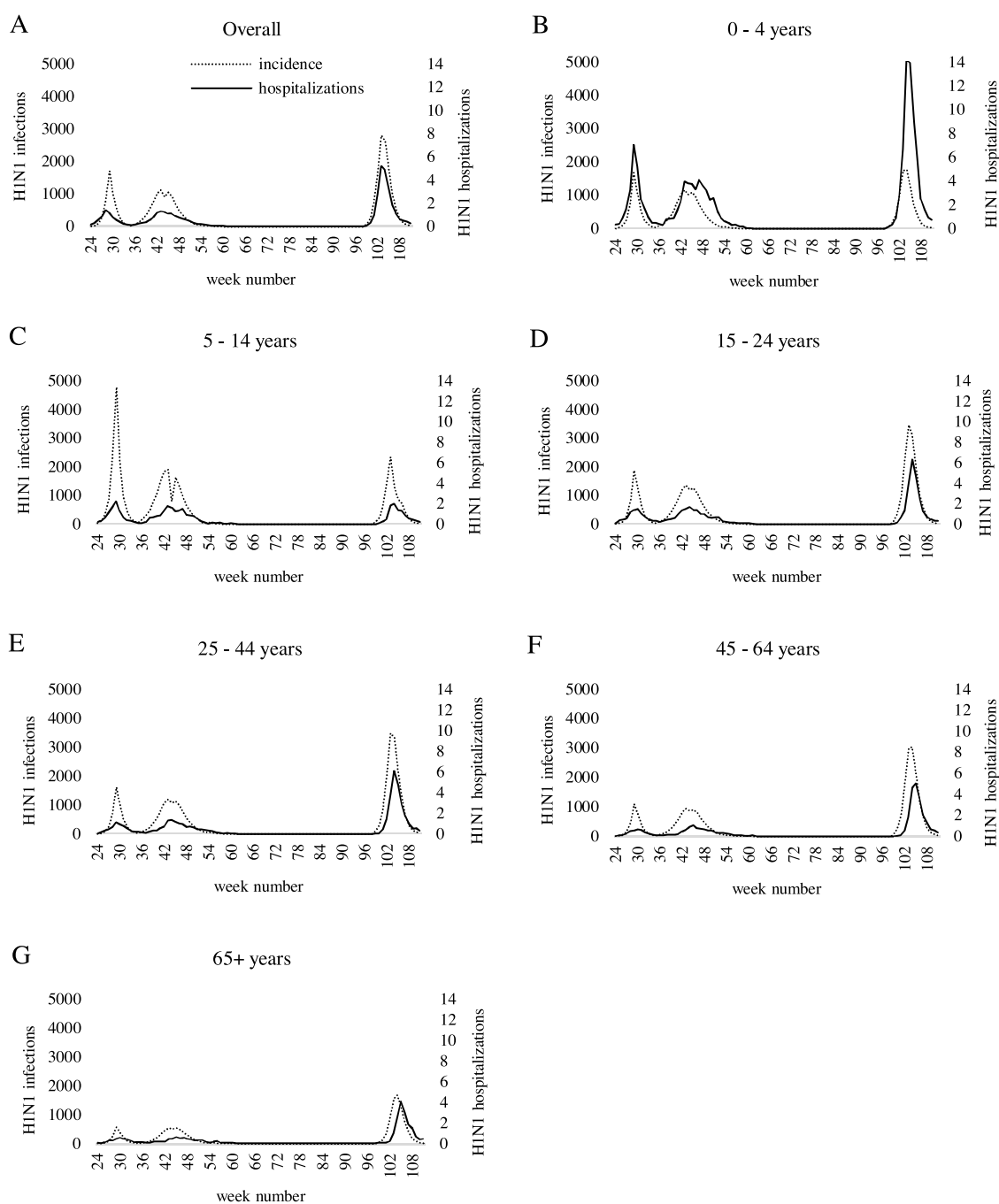


Figure 1. H1N1 infection incidence (dotted line – left y-axis) and H1N1 hospitalizations (solid line – right y-axis), weeks between June 2009 and February 2011.

Note: Incidence data is estimated with influenza transmission mathematical models using Bayesian inference from Dorigatti and colleagues¹⁴. Hospitalizations are estimated as the number of ILI hospitalizations in excess of SARIMA-estimated non-pandemic hospitalizations and therefore due to H1N1 from Lau and colleagues¹⁵. Both incidence and hospitalizations are standardized per 100,000 relative to the population of each respective age-group.

Data includes the 2009 pandemic and 2010/11 post-pandemic influenza season overall and by age-group.

number of hospitalizations was higher (Figure 2A & B). This implies a higher hospitalization rate in the post-pandemic than the pandemic period for all ages in total: 185.9 (95% CI 182.2–188.1) compared to 139.2 (95% CI 130–144.4), respectively (Figure 2C). Those aged 0–4-years-old had a significantly higher hospitalization rate than all other ages during the pandemic and post-pandemic period with 455.4 (95% CI 416.8–497) and 755.7 (95% CI 745.3–764.7), respectively. Elderly aged 65-years-old and over had the second highest hospitalization rates at 143.4 (95% CI 103.1–167.9) and 218.2 (95% CI 211.2–218.5) for the pandemic and post-pandemic flu season, respectively.

The post-pandemic influenza season was more severe than the pandemic across all four severity measures and for all ages combined. The post-pandemic flu season had statistically significantly higher overall aLOS, number of ventilation, pneumonia, and death-associated H1N1 hospitalizations (Figure 3), and ventilation and pneumonia-associated H1N1 hospitalization rates (Figure 4) than the pandemic.

While children had the highest absolute severity during the pandemic and post-pandemic period compared to other age-groups, adults had the highest rates of hospitalized severity. Those aged 0–4-years-old had significantly higher population standardized number of ventilation and pneumonia hospitalizations in both periods than most other age-groups

(Appendix Table A3). Adults aged 45–64-years-old, however, had the highest hospitalization-standardized ventilation and pneumonia rates (Appendix Table A4). The elderly aged 65-years-old and over had the second highest ventilation and pneumonia hospitalization rates for both time periods.

Comparisons within each age-group further demonstrated that for most age-groups, the pandemic was significantly less severe than the post-pandemic period in terms of aLOS, ventilation, and ventilation hospitalization rates. Number of pneumonia hospitalizations and pneumonia hospitalization rates were split between the younger and older populations. Those younger than 25-years-old had greater population-standardized H1N1-associated pneumonia hospitalizations during the pandemic compared to the post-pandemic period, while those older than 25-years-old exhibited the opposite trend (i.e. post-pandemic H1N1 pneumonia hospitalization numbers were greater than pandemic numbers) (Appendix Table A3). However, we found flipped results when examining hospitalization-standardized pneumonia rates: those younger than 15-years-old had higher rates during the post-pandemic period and patients 15-years-old and over had higher rates during the pandemic (Appendix Table A4).

We found that H1N1 fatalities were significantly higher during the post-pandemic flu season than during the pandemic: 1.09 (95% CI 1.01–1.16) compared to 0.57 (95% CI 0.37–0.77) deaths per

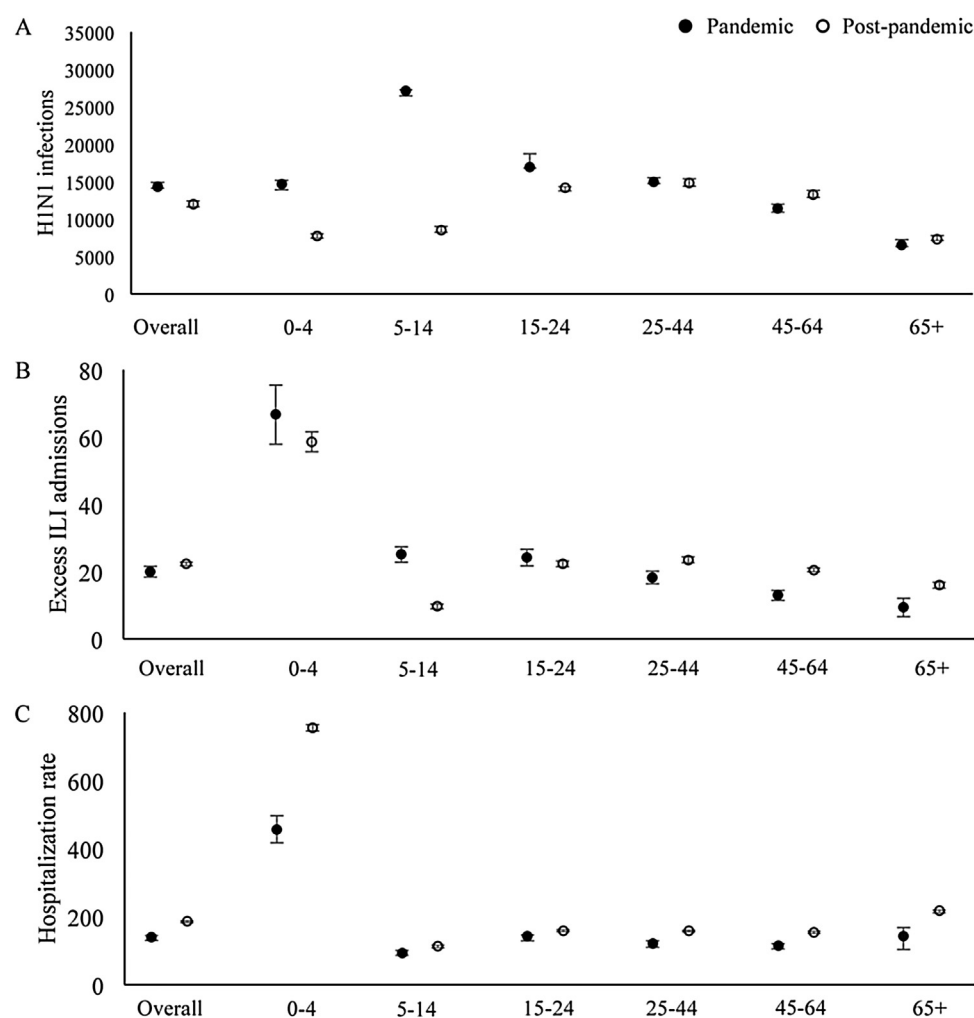


Figure 2. H1N1 infections (A), H1N1 hospitalizations (B), and H1N1 hospitalization rates (C), population standardized.

Notes: 95% CI displayed for all values. H1N1 infections and hospitalizations standardized per 100,000 population for age-groups and all ages. 2009 pandemic (solid circle) and 2010/11 post-pandemic influenza season (hollow circle). Hospitalization rates are calculated as H1N1 hospitalizations divided by H1N1 infections, then multiplied by 100,000 to give the number of H1N1 hospitalizations per 100,000 H1N1 infections.

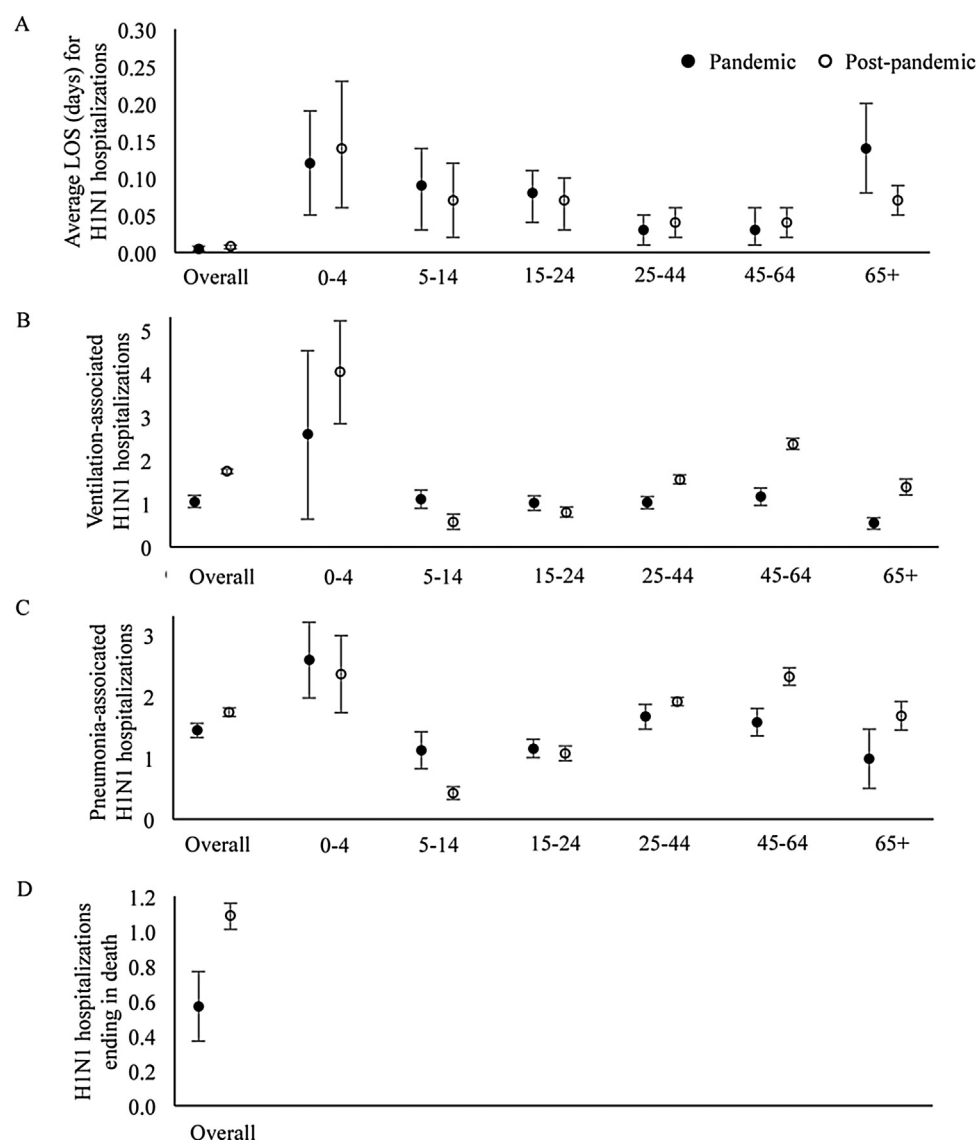


Figure 3. Average length of stay (LOS) for H1N1 hospitalizations (A); H1N1 hospitalizations requiring ventilation (B), diagnosed with pneumonia (C), and ending in death (D), population standardized.

Notes: Values with 95% CI band. Each severity measure (average length of stay for H1N1 hospitalizations, H1N1 hospitalizations requiring ventilation, diagnosed with pneumonia, and resulting in deaths) standardized by 100,000 population in applicable age-groups and overall. 2009 pandemic (solid circle) and 2010/11 post-pandemic influenza season (hollow circle).

100,000 population, respectively (Figure 3D). Mortality rates were also higher for all other indicators during the post-pandemic influenza season compared to the pandemic (Figure 4C–F). Infection fatality rates were 4.01 (95% CI 2.62–5.21) versus 9.07 (95% CI 8.68–9.34) deaths and hospitalization fatality rates 2876 (95% CI 2047–3551) versus 4877 (95% CI 4647–5094) deaths per 100,000 infections for the pandemic versus post-pandemic periods (Appendix Table A4). Ventilation and pneumonia fatality rates were particularly high at 55,130 (95% CI 41,294–65,415) and 62,163 (95% CI 59,968–64,176) deaths per 100,000 H1N1 hospitalizations utilizing ventilation, and 39,658 (95% CI 27,809–49,566) and 62,197 (95% CI 60,401–63,824) deaths per 100,000 H1N1 hospitalizations with pneumonia during the pandemic and post-pandemic periods, respectively.

During the pandemic, hospitalizations for those aged 25-years-old and over lagged incidences of infection by one week (Table 3) with variations up to 10 weeks around central estimates (Figure 5), suggesting a one-week delay between symptoms onset and hospitalization. No lag was exhibited between infection incidence

and hospitalization for ages younger than 25-years-old. During the post-pandemic influenza season, however, hospitalizations lagged infections by at least one week for each age-group with a lower variation of up to 8 weeks around the central estimate (Table 3 and Figure 6). For those 65-years-old and over, hospitalizations lagged infections by two weeks, suggesting an average two-week time lag between symptoms onset and hospitalization.

Discussion

Although the overall infection incidence was higher in the pandemic than the post-pandemic period, hospitalization rates were greater in the post-pandemic period. This suggests that in the post-pandemic influenza season, despite fewer H1N1 infections, patients were more likely to present to the hospital. A self-protection fatigue effect, where anxieties surrounding the disease relax over time making individuals more vulnerable to infection (Chen et al., 2013), and/or mutations to increase viral transmissibility and fitness (Dorigatti et al., 2013; Elderfield et al., 2014) may

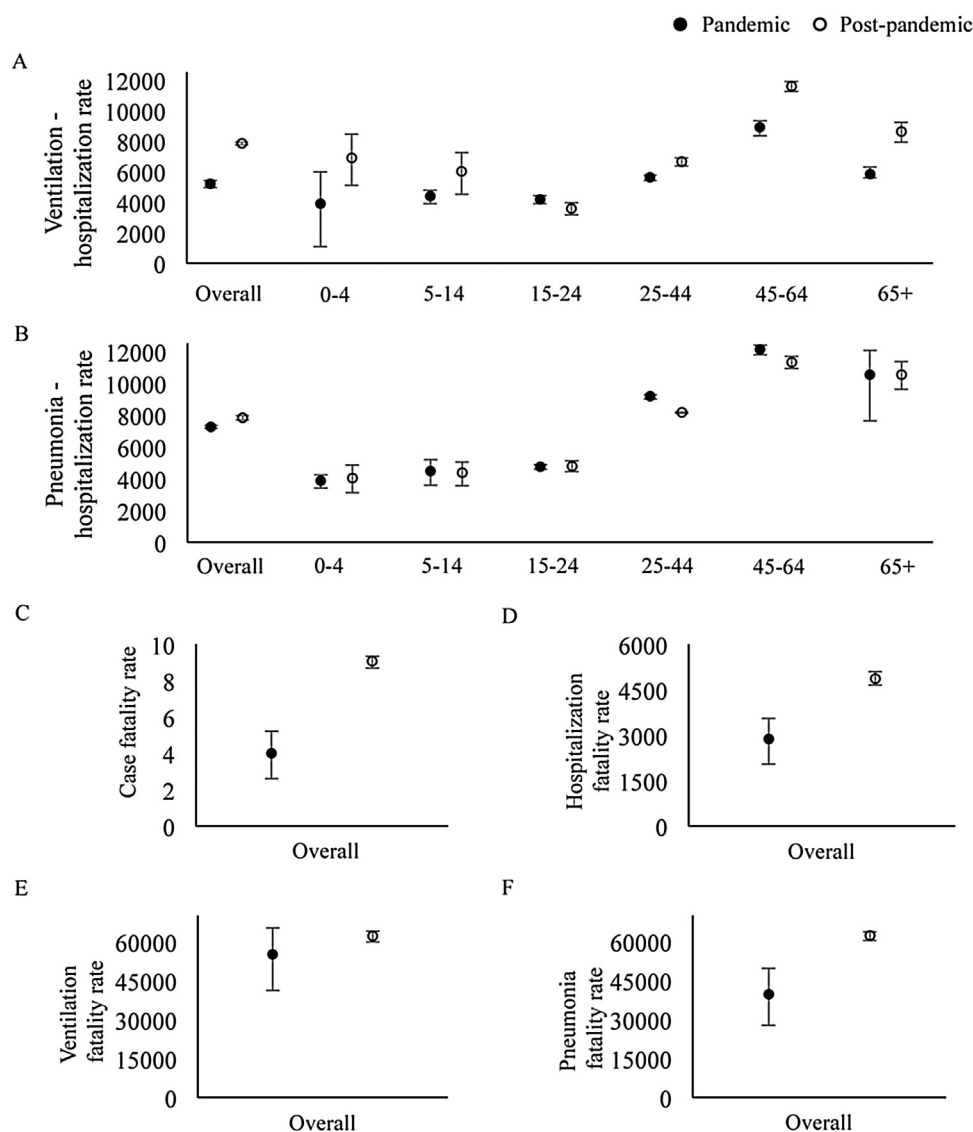


Figure 4. Ventilations (A), and pneumonia co-morbidity (B) per 100,000 H1N1 hospitalizations; Infection (C) hospitalization (D) ventilation (E) and pneumonia (F) fatality rates.

Notes: Ventilation and pneumonia-hospitalization rates calculated as number of ventilations and pneumonia-associated H1N1 hospitalizations divided by H1N1 hospitalizations, then multiplied by 100,000.

Fatality rates calculated as H1N1 inpatient deaths divided by H1N1 incidence (case fatality rate), H1N1 hospitalizations (hospitalization fatality rate), ventilation-associated H1N1 hospitalizations (ventilation fatality rate), and pneumonia-associated H1N1 hospitalizations (pneumonia-fatality rate), then multiplied by 100,000.

Estimates calculated by age-group (A&B only) and overall across the 2009 pandemic (solid circle) and 2010/11 post-pandemic influenza season (hollow circle).

Table 3

Time lags between H1N1 hospitalizations and incidence (weeks).

Age Group	2009 pandemic (June 8, 2009 to March 7, 2010)	2010/11 post-pandemic influenza season (November 22, 2010 to February 20, 2011)
Overall	+1	0
0–4	0	–1
5–14	0	–1
15–24	0	–1
25–44	–1	–1
45–64	–1	–1
65+	–1	–2

Notes: A lag of 0 suggests hospitalization do not lag incidence, a lag of –1 suggests hospitalizations lag incidence by 1 week, a lag of –2 suggests hospitalizations lag incidence by 2 weeks, and a lag of +1 suggests incidence lag hospitalization by 1 week.

Time series from temporal cross-correlation analysis during the 2009 H1N1 pandemic and 2010/11 post-pandemic influenza season overall and by age-group.

help explain why more hospitalizations occurred despite having fewer infections in the post-pandemic period.

Furthermore, cross-correlation analysis suggests that lags between incidence and hospitalization were shorter during the pandemic than the post-pandemic flu season, where those who were infected waited one to two weeks before presenting to the hospital. We also found higher severity per infection/hospitalization during the post-pandemic period. This may indicate that during the pandemic, individuals presented to the hospital sooner after infection and may have been less severe to treat after arrival. Conversely, those who were hospitalized during the post-pandemic flu season may have had more complications and higher severity requiring more intensive and costlier treatment due to delayed hospitalization.

Our finding that children aged 0–4 years-old had the greatest hospitalization rates across both time periods is consistent with previous studies (Lau et al., 2019).

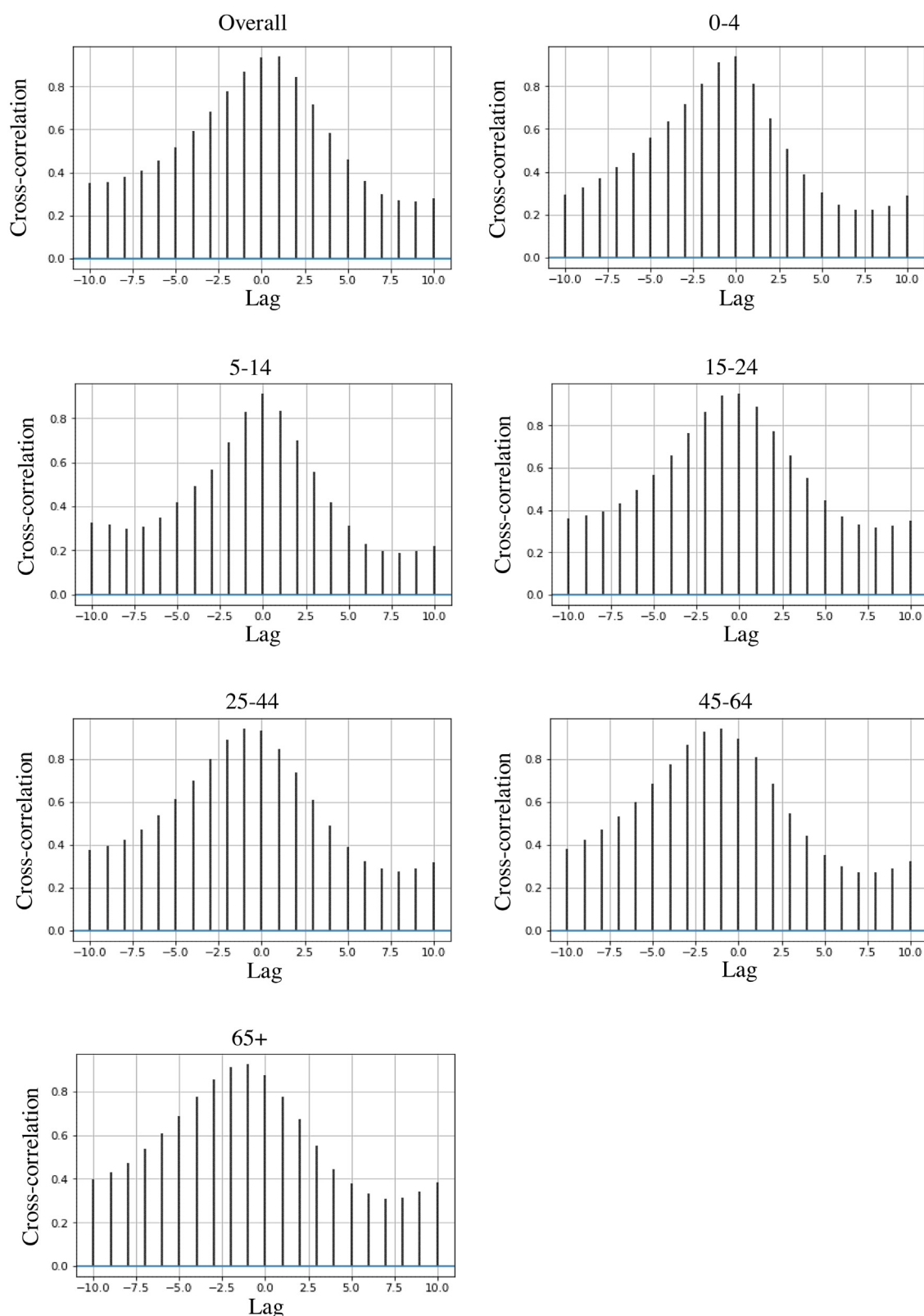


Figure 5. Cross-correlation plots between H1N1 incidence and H1N1 hospitalizations, 2009/10 pandemic (June 8, 2009 to March 7, 2010).
 Note: 10 weeks before and after lags are used.

Interestingly, however, adults aged 45–64-years-old had the highest ventilation and pneumonia-associated H1N1 hospitalization rates of all age-groups across both pandemic and post-pandemic periods. They were followed by the elderly aged 65-

years-old and over and then young adults aged 25–44-years-old. This suggests that while children may be the most hospitalized age-group, adults were the most severe and utilized the most resources once hospitalized.

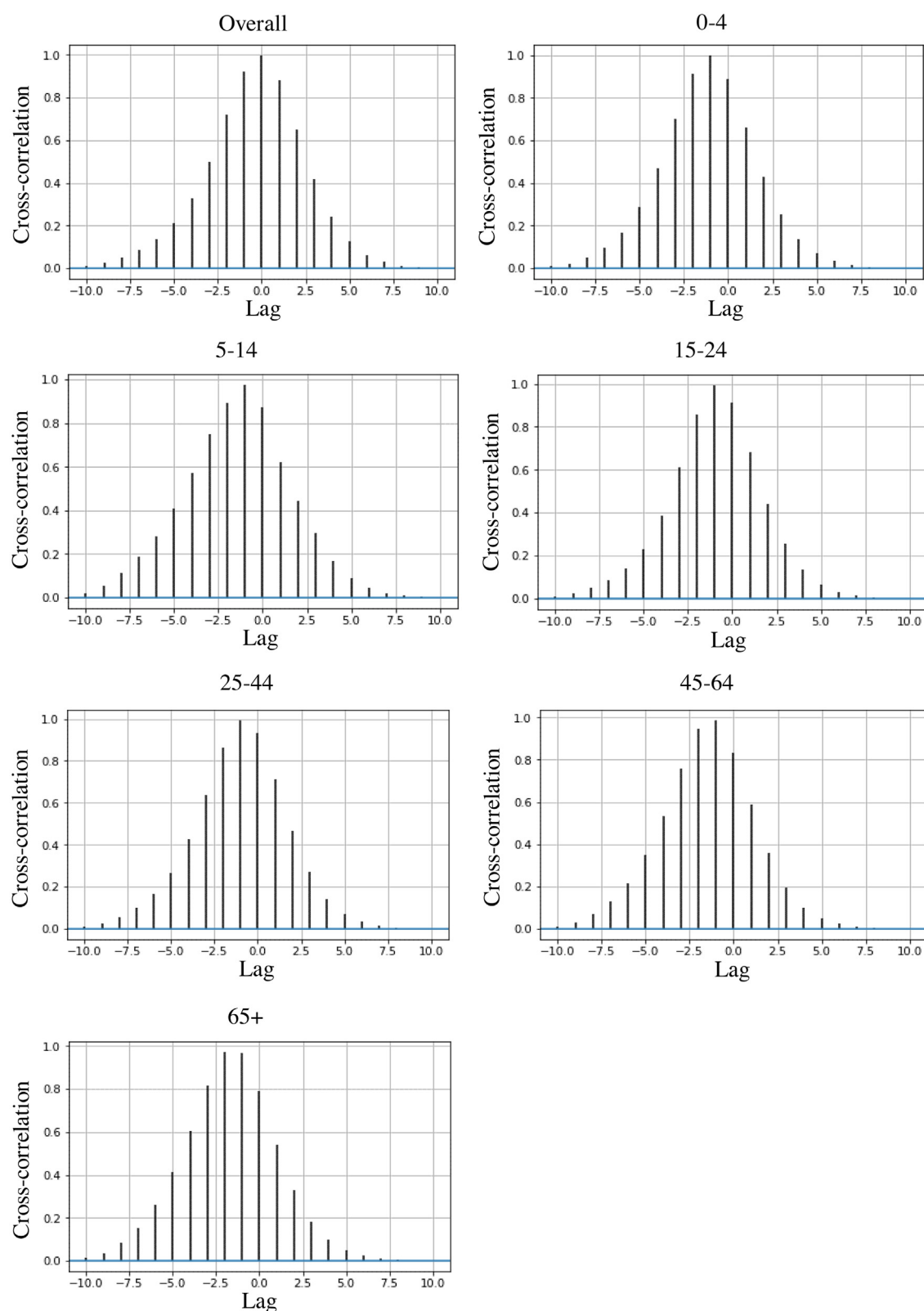


Figure 6. Cross-correlation plots between H1N1 incidence and H1N1 hospitalizations, 2010/11 post-pandemic (November 22, 2010 to February 20, 2011). Note: 10 weeks before and after lags are used.

The higher severity in adults across both time periods aligns with the longer lags between incidence and hospitalization seen in older versus younger individuals. One possibility is that fever, a common ILI symptom, may not always manifest in elderly and

immunosuppressed individuals (Centers for Disease Control and Prevention, 2019) and is less present in adults than children (Chughtai et al., 2017). Therefore, adults and elderly may not have been aware that they were infected until later compared to

younger individuals, which may have contributed to wider spreading of the disease as well as helped explain their delayed and more severe presentation to the hospital.

This study is not without limitations. Case fatality rates were calculated using deaths from ILI hospitalizations and did not include deaths that may have occurred outside of hospitals. Therefore, we may have underestimated the true case fatality rates. Additionally, SARIMA relies on past observations to predict future values and thus is unable to capture any unobserved factors that may have impacted the number and severity of ILI hospitalizations but are unrelated to the pandemic. Furthermore, our use of diagnosis codes to determine ILI hospitalizations suggests that our data is subject to the interpretation of physicians and potential misdiagnosis of ILI as another respiratory disease or vice versa.

Nevertheless, our estimates of H1N1 hospitalization rates, hospitalization severity rates, mortality rates, and lags between incidence and hospitalization can help policymakers devise strategies to mitigate the effects of the ongoing COVID-19 pandemic and plan for future influenza pandemics. These findings suggest that while emphasis on capacity planning and resource allocation during the pandemic is needed, we should also focus on the post-pandemic period as that has the potential to overwhelm health systems even more than the pandemic. Our analysis of the H1N1 data suggests that despite having fewer cases, the hospitalization rate was 34% higher and severity rates were 20–90% greater for those hospitalizations in the post-pandemic influenza season compared to the pandemic, which may strain health systems that are unprepared and unequipped to deal with these surges. A reduction in the lags between incidence and hospitalization during the post-pandemic period may help reduce burdens on hospitals as patients may be less severe and utilize fewer resources once admitted. This study illustrates that analyses using large-scale surveillance data connecting mathematical modelling and statistical methods linking time series of the incidence of infection, hospitalization, severity, and death can inform the public health response to health emergencies.

As this study is conducted at the national level, future studies that disaggregate analysis at a regional or hospital level may identify any heterogeneity in impact due to differences in capacity levels across various geographical areas. This can help policymakers focus on some locations that are more likely to be overwhelmed during pandemics. Second, further assessment regarding how capacity-constrained hospitals potentially trade-off caring for non-pandemic and pandemic patients over the course of pandemics can help hospital planners and policymakers devise strategies to minimize the burden for all patient types. Finally, further exploration into the heterogeneity in lags between infections and hospitalizations across age-groups and pandemic and post-pandemic periods may help policymakers integrate early interventions (e.g. expanding primary care) into their preparedness plans.

Conclusion

Countries that focus on pandemic preparedness can better cope with unanticipated demand and implement coordinated policies and strategies to mitigate the burden of pandemics on health systems. Governmental health organizations across the globe, including the World Health Organization and the United Kingdom's Department of Health and Social Care, have emphasized the need for pandemic preparedness through better response capabilities and disease surveillance as well as more effective screening, diagnosis, and treatment (Department of Health Pandemic Influenza Preparedness Team, 2011; World Health Organization, 2011, 2018, 2019).

The COVID-19 pandemic has proven that policymakers need better understanding regarding how pandemics propagate

through health systems across time. Although COVID-19 differs from H1N1 across many aspects, including the most-affected age-groups, mortality rates, and scale of the outbreak, our findings demonstrate how collecting widespread data on infections and hospitalizations and implementing time series econometric methods can help governments manage their response to pandemics. Real-time access to hospital and surveillance data is often lacking during pandemics. However, our study demonstrates how this data can be used to inform effective hospital response in order to provide the best care possible.

Experience with the 2009 H1N1 pandemic has shown that hospitalizations and mortality were higher in the post-pandemic winter of 2010/11 than during the actual pandemic in 2009/10 (Lau et al., 2019). Our results further highlight that surveillance and assessment of post-pandemic admissions is essential to ensure that health systems address care needs and mortality and morbidity are mitigated. Policymakers need to remain vigilant now and during future influenza pandemics, as there are often multiple waves of infections with novel influenza viruses, even after the official end of the pandemic.

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Conflicts of interest

We declare that we have no conflicts of interest.

Ethical approval

The authors declare that ethical approval was not required for this study.

Contributions

KL undertook the estimation and analysis. ID and KH conceived the research idea; KL and MM contributed to the research idea. KL wrote most of the paper. All authors contributed to preparing the data, analysis, and writing/editing the manuscript.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.ijid.2021.01.070>.

References

Bolotin S, Pebody R, White PJ, McMenamin J, Perera L, Nguyen-Van-Tam JS, et al. A new sentinel surveillance system for severe influenza in England shows a shift

- in age distribution of hospitalised cases in the post-pandemic period. *PLoS One* 2012;7:e30279, doi:<http://dx.doi.org/10.1371/journal.pone.0030279>.
- Box GE, Jenkins GM, Reinsel GC, Ljung GM. Time series analysis, control, and forecasting. 5th ed. New Jersey: John Wiley & Sons; 2015.
- Campbell C, Mytton O, McLean E, Rutter P, Pebody R, Sachedina N, et al. Hospitalization in two waves of pandemic influenza A (H1N1) in England. *Epidemiol Infect* 2011;139:1560–9, doi:<http://dx.doi.org/10.1017/S0950268810002657>.
- Capelastegui A, Quintana J, Bilbao A, España P, Garin O, Alonso J, et al. Score to identify the severity of adult patients with influenza A (H1N1) 2009 virus infection at hospital admission. *Eur J Clin Microbiol Infect Dis* 2012;31:2693–701.
- Centers for Disease Control and Prevention. Clinical Signs and Symptoms of Influenza 2019. <https://www.cdc.gov/flu/professionals/acip/clinical.htm> (Accessed 23 March 2020).
- Chen F, Griffith A, Cottrell A, Wong YL. Behavioral responses to epidemics in an online experiment: using virtual diseases to study human behavior. *PLoS One* 2013;8:e52814, doi:<http://dx.doi.org/10.1371/journal.pone.0052814>.
- Chughtai A, Wang Q, Dung T, Macintyre C. The presence of fever in adults with influenza and other viral respiratory infections. *Epidemiol Infect* 2017;145:148–55.
- Cockburn H. Italian doctors urge UK to prepare for impact of coronavirus as footage shows A&E overrun with patients. 2020 *The Independent*. <https://www.independent.co.uk/news/world/europe/coronavirus-italy-footage-video-hospital-bergamo-covid-19-a9414136.html> (Accessed 2 April 2020).
- Department of Health Pandemic Influenza Preparedness Team. UK Influenza Pandemic Preparedness Strategy 2011 London. 2011.
- Dorigatti I, Cauchemez S, Ferguson NM. Increased transmissibility explains the third wave of infection by the 2009 H1N1 pandemic virus in England. *Proc Natl Acad Sci USA* 2013;110:13422–7, doi:<http://dx.doi.org/10.1073/pnas.1303117110>.
- Elderfield RA, Watson SJ, Godlee A, Adamson WE, Thompson CI, Dunning J, et al. Accumulation of human-adapting mutations during circulation of A (H1N1) pdm09 influenza virus in humans in the United Kingdom. *Journal of Virology* 2014;88:13269–83.
- Feuer W. New York City hospitals are nearly 'maxed out,' former FDA chief says. *CNBC*; 2020. <https://www.cnbc.com/2020/03/25/new-york-city-hospitals-are-nearly-maxed-out-former-fda-chief-says.html>.
- Hendriks W, Boshuizen H, Dekkers A, Knol M, Donker GA, van der Ende A, et al. Temporal cross-correlation between influenza-like illnesses and invasive pneumococcal disease in The Netherlands. *Influenza Other Respir Viruses* 2017;11:130–7.
- Huang F, Zhou S, Zhang S, Wang H, Tang L. Temporal correlation analysis between malaria and meteorological factors in Motuo County, Tibet. *Malar J* 2011;10:54.
- Kaseltz TB, Martin ET, Power LE, Cinti S. Impact of vaccination on morbidity and mortality in adults hospitalized with influenza A, 2014–2015. *Infect Dis Clin Pract* 2019;27:328–33.
- Kwok KO, Riley S, Perera RA, Wei VW, Wu P, Wei L, et al. Relative incidence and individual-level severity of seasonal influenza A H3N2 compared with 2009 pandemic H1N1. *BMC Infect Dis* 2017;17:337.
- Lau K, Hauck K, Miraldo M. Excess influenza hospital admissions and costs due to the 2009 H1N1 pandemic in England. *Health Econ* 2019;28:175–88.
- Liu XX, Qin G, Li X, Zhang J, Zhao K, Hu M, et al. Excess mortality associated with influenza after the 2009 H1N1 pandemic in a subtropical city in China, 2010–2015. *Int J Infect Dis* 2017;57:54–60.
- Louie JK, Acosta M, Winter K, Jean C, Gavali S, Schechter R, et al. Factors associated with death or hospitalization due to pandemic 2009 influenza A (H1N1) infection in California. *JAMA* 2009;302:1896–902, doi:<http://dx.doi.org/10.1001/jama.2009.1583>.
- MacIntyre CR, Chughtai AA, Barnes M, Ridda I, Seale H, Toms R, et al. The role of pneumonia and secondary bacterial infection in fatal and serious outcomes of pandemic influenza a (H1N1) pdm09. *BMC Infect Dis* 2018;18:1–20.
- Maleki M, Mahmoudi MR, Wraith D, Pho KH. Time series modelling to forecast the confirmed and recovered cases of COVID-19. *Travel Med Infect Dis* 2020;37:101742.
- Maves RC, Jamros CM, Smith AG. Intensive care unit preparedness during pandemics and other biological threats. *Crit Care Clin* 2019;35:609–18.
- Mueller B. U.K. Hospitals, a Desperate Battle Against a Threat Many Saw Coming. *The New York Times*; 2021. <https://www.nytimes.com/2021/01/21/world/europe/uk-hospitals-covid-variant.html>.
- Mytton O, Rutter P, Donaldson L. Influenza A (H1N1) pdm09 in England, 2009 to 2011: a greater burden of severe illness in the year after the pandemic than in the pandemic year. *Euro Surveill* 2012;17:20139.
- Office for National Statistics, National Records of Scotland, & Northern Ireland Statistics and Research Agency. 2011 Census Aggregate Data. <https://www.ons.gov.uk/census/2011census>.
- Presanis A, Pebody R, Paterson B, Tom B, Birrell P, Charlett A, et al. Changes in severity of 2009 pandemic A/H1N1 influenza in England: a Bayesian evidence synthesis. *Br Med J* 2011;343:d5408.
- Qin A. China pledged to build a new hospital in 10 days. It's close. *The New York Times*; 2020. <https://www.nytimes.com/2020/02/03/world/asia/coronavirus-wuhan-hospital.html>.
- Reed C, Angulo FJ, Swerdlow DL, Lipsitch M, Meltzer MI, Jernigan D, et al. Estimates of the prevalence of pandemic (H1N1) 2009, United States, April–July 2009. *Emerg Infect Dis* 2009;15:2004.
- Shrestha SS, Swerdlow DL, Borse RH, Prabhu VS, Finelli L, Atkins CY, et al. Estimating the burden of 2009 pandemic influenza A (H1N1) in the United States (April 2009–April 2010). *Clin Infect Dis* 2011;52:S75–82, doi:<http://dx.doi.org/10.1093/cid/ciq012>.
- Thompson WW, Weintraub E, Dhanekar P, Cheng PY, Brammer L, Meltzer MI, et al. Estimates of US influenza-associated deaths made using four different methods. *Influenza Other Respir Viruses* 2009;3:37–49.
- World Health Organization. Pandemic influenza preparedness framework. Geneva: WHO; 2011.
- World Health Organization. Managing epidemics: key facts about major deadly diseases. Geneva: WHO; 2018.
- World Health Organization. Global influenza strategy 2019–2030. Geneva: WHO; 2019.
- Wu S, Wei Z, Greene C, Yang P, Su J, Song Y, et al. Mortality burden from seasonal influenza and 2009 H1N1 pandemic influenza in Beijing, China, 2007–2013. *Influenza Other Respir Viruses* 2017;12:88–97.